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FISH & RICHARDSON P.C.
PO BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 12/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/705,245	CHEN ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09/18/2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 6-25* is/are pending in the application.

4a) Of the above claim(s) *7 and 13-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 6, 8-12, and 20-25* is/are rejected.

7)☒ Claim(s) *1, 12 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/4/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3, and 6-25 are pending.

Claims 2, 4, and 5 are cancelled.

Claims 7, and 13-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claim 7 is drawn to a non-elected drug and non-elected allele; Claims 13-19 are drawn to a non-elected invention.

Claims 1, 3, 6, 8-12, and 20-25 are examined on the merits.

This Office Action is in reply to Applicants' correspondence of 09/182006. Claims 2, 4, and 5 are cancelled; claims 7, and 13-19 are withdrawn; no claims have been newly added; claims 1 and 20 have been amended. Applicants' remarks, Declaration, and amendments have been fully considered but are not found to be persuasive. No new grounds of rejection are presented in this Office Action. Any rejections or objections not reiterated herein have been withdrawn. This Action is made FINAL.

IDS of Feb 4, 2006

Applicant has noted in the Remarks that the cited US Patent 6,583,139 on the PTO-1449 filed 2/4/06 was not initialed with the copy of that PTO-1449 that was supplied with the Office Action of 5/17/06. The form with the cited reference initialed as considered by the Examiner is included with this Office Action.

Claim Objections

1. Claims 1, 12 and 20 are objected to as specifically reciting non-elected subject matter. The Requirement for Restriction set forth on 03/02/2006 resulted in the election of claims as pertaining to HLA-B*1502, carbamazepine, and Cw*0801. The claims specifically recite non-elected alleles (HLA-B* 5801 and 4601), drugs (phenytoin), and equivalent genetic markers (HLA-DRB1*1202, CW*0806, A*1101, MICA*019, and

Cw*0302). Prior to allowance, non-elected subject matter will be required to be deleted from the claim.

Claim Rejections - 35 USC § 112 1st Enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 3, 6, 8-12, and 20-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for assessing the risk of a Taiwanese patient for developing Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN) in response to carbamazepine (CBZ) comprising determining the presence of an HLA-B*1502 allele or an HLA-Cw*0801 allele wherein presence of the allele is indicative of an increased risk for SJS/TEN, does not reasonably provide enablement for assessing the risk of any other adverse reactions in response to any other drugs in any other human population using any equivalent genetic marker. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The claims are drawn to a method for assessing in a human patient the risk of an adverse drug reaction in response to a drug by determining the presence of the

HLA-B*1502, wherein the presence of the allele is indicative of a risk for an adverse reaction.

The claims encompass assessing risk in a patient from any population or of any ethnic background.

Claims 20-25 encompass adverse drug reaction in response to any drug.

Claims 20-25 encompass any adverse drug reaction.

Claim 11 encompasses the use of any equivalent genetic marker.

The nature of the invention requires knowledge of a relationship between HLA-B*1502 or an equivalent genetic marker and the risk of an individual to develop an adverse reaction in response to a drug.

Direction provided by the specification and working example

The specification of the instant application teaches an analysis of HLA-B allele genotype and the development of adverse drug reaction.

The specification teaches that there are various types of adverse drug reactions, and broadly defines 'adverse drug reaction' as an undesired or unintended effect of a drug (p.8, ln.1). The specification teaches that drug eruptions may be mild to moderate in nature (macuolpapular rash, erythema mulitforme, urticaria, fixed drug eruption) or more severe (SJS, TEN) (p.4 lns.10-17).

The specification teaches that there is evidence that adverse drug reactions involve MHC-restricted presentation of drug or drug metabolites.

The specification provides an example of a case:control analysis of HLA-B genotypes and adverse drug reactions in a Taiwanese population. The specification

teaches that the 'cases' were 238 individuals with ADRs, wherein 112 patients were diagnosed with SJS/TEN adverse drug reactions (defining this adverse drug reactions as: SJS is skin detachment of less than 10% of body-surface area; overlap SJS-TEN as 10-30%; TEN as greater than 30%; where SJS, overlap SJS-TEN, and TEN are collectively referred to as SJS/TEN (p. 28, lns 6-15), and 126 individuals had milder reactions to various drugs (p.30 – Example 1). Of the 112 SJS/TEN cases, 42 had carbamazepine-induced SJS/TEN (p.28 ln.6). Controls for the analysis provided in the example were 73 carbamazepine-tolerant patients, and 94 non-patients form the general population (p.28 lns.16-21).

The specification teaches the genotyping of subjects' HLA alleles using PCR amplification with sequence specific oligonucleotides and hybridization of the amplification product to a lineblot (p.28 lns.24-30).

The specification provides an analysis of HLA alleles present in patients with carbamazepine –induced SJS/TEN as compared to patients with milder reactions, the general population, and carbamazepine-tolerant patients (Table 1; p.30 ln.29 – p.31 ln.16). The specification teaches that HLA*B-1502 was detected in 42 of 42 SJS/TEN patients who received carbamazepine, but found only in 3 of 73 carbamazepine tolerant patients, 9 of 142 patients with mild adverse reactions, and 5 of 94 general population subjects. The results indicate that the HLA*B-1502 allele is related to carbamazepine – induced SJS/TEN in a statistically significant fashion (Table 1).

The specification does not provide any analysis of any non-Taiwanese population.

The specification does not teach that the HLA-B*1502 allele is associated, in a statistically significant fashion, with any adverse reactions other than SJS/TEN, or with reactions to drugs other than carbamazepine.

The specification teaches that 38 of the 42 carbamazepine-induced SJS/TEN patients also had the HLA-Cw*0801 allele. The specification does not provide any statistical analysis of the association of HLA-Cw*0801 with carbamazepine-induced SJS/TEN, nor any analysis of linkage between HLA-B*1502 and HLA-Cw*0801.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art with regard to identification of a particular HLA-B allele is well developed, and the level of skill in the art of identification of an adverse drug reaction is high, the level of unpredictability with regard to the association of a particular HLA-B allele with an adverse drug reaction is even higher as evidenced by the prior art, post-filing art, and the specification of the instant application.

The specification teaches only the analysis of a Taiwanese population. It is unpredictable as to whether or not HLA-B*1502 would be indicative of risk of an adverse drug reaction in another population. The post filing art of Hung et al (2005) teaches an analysis of HLA-B genotyping to detect carbamazepine-induced SJS. The reference teaches that alleles may be present in different frequencies in different populations, and that it is more likely to find a positive result when a study is conducted in a population with a high frequency of the allele (p.233, left col., lns.8-13). Additionally, the reference teaches that as study results can vary between study populations, it remains to be seen to what extent the association between HLA-B*1502 and CBZ-induced SJS/TEN applies

to other populations (p.233, right col., lns. 11-16). Furthermore, the post filing art of Lonjou et al (2005) indicates that HLA-B*1502 is not a useful prediction marker of CBZ related SJS in the European population (p.3, left col., second paragraph).

The instant specification teaches the unpredictability in using HLA-B*1502 to assess drug reactions other than SJS/TEN induced by carabamazepine. The specification teaches, for example, that HLA-B*1502 was not detected in 16 patients suffering from milder cutaneous reactions to carbamazepine (Table 2; p.31 lns.11-13). Additionally, a drug information sheet for carbamazepine (Carbamazepine, 2006) indicates that there is a wide variety of side effects (which are adverse drug reactions) related to carbamazepine (p.2 – Side effects) for which there is no data presented in the specification.

And while the specification indicates that the HLA-B*1502 allele was found in 17 of 53 SJS/TEN patients who received drugs other that carbamazepine, the specification presents no measure of the statistical significance of these results. The prior art of Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant. Thisted teaches that it has become scientific convention to say that a p-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion. Additionally, the prior art of Leeder (1998) (as cited in the IDS) teaches that the mechanism of drug hypersensitivity is based on the production of reactive metabolites from the particular drug of interest (Fig 1; p.S9, left col., "Hapten Hypothesis"). The reference teaches that

different drugs create different metabolites (p.S10 – Bioactivation of PHT and CBZ to reactive intermediates). Thus it is unpredictable as to whether or not HLA-B*1502 can be used in assessing risk of an adverse reaction to a drug other than carbamazepine.

It is unpredictable as to whether or not the presence of any 'equivalent genetic marker' is useful for determining the presence of the HLA-B*1502 allele or for the assessment of risk of drug adverse reaction. While the specification teaches that 38 of 42 carbamazepine-induced SJS/TEN patients had an HLA-Cw*0801 allele, there is no statistical analysis of the significance of the association of HLA-Cw*0801 with carbamazepine-induced SJS/TEN, nor any analysis of the linkage of HLA-B*1502 with HLA-Cw*0801. Regarding the linkage of HLA-B*1502 with HLA-Cw*0801, Deng et al (2001) teaches that the traditional criteria are that a Logarithm-of -Odds (LOD) score of > 3.0 is taken as evidence for a significant linkage, a LOD score < -2.0 is taken as evidence against linkage, and a LOD score between -2.0 and 3.0 is not conclusive concerning linkage and exclusion for the genomic region under test (p.314, first full paragraph).

Quantity of experimentation required

A large and prohibitive amount of experimentation would have to be performed in order to use the inventions in the full scope of the claims. One would have to perform case:control studies to establish that HLA-B*1502 is associated in a statistically significant fashion with any different adverse reaction in a patient in response to any different drug. One would also have to establish that any associations are applicable to any different patient population of interest.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the paucity of working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope in which it is claimed.

Response to Remarks

Applicants Remarks and Declaration have been fully and carefully considered but are not found to be persuasive.

Applicants argue that amended claim 1 is directed to a method for assessing the risk of a human patient for developing an adverse drug reaction in response to a drug by determining the presence of an HLA-B allele selected from the group consisting of HLA-B* 1502, 5801, and 4601, wherein presence of the allele is indicative of risk for SJS/TEN in response to the drug CBZ or phenytoin.

Initially it is noted, as addressed in the Claim Objection earlier in this Office Action, that in Response to the Requirement for Restriction of 04/03/2006, applicant has elected for the examination of claims insofar as they specifically require the 1502 allele, CBZ, and the Cw*0801 allele.

Concerning the breadth of the currently presented claims, it is also noted that the claims are still generic with regard to the detection of an equivalent genetic marker (e.g. claim 11), and generic with regard to drugs and adverse reactions (e.g. claim 20, from

which claims 21-25 depend). The rejection of claims under 35 USC 112 1st¶ for lack of enablement has set forth that such generic claims are not enabled for their full scope. Furthermore, the recitation in claim 1 of "determining the presence of an HLA-B allele selected from the group consisting of HLA-B*1502" has been interpreted as including methods which directly detect the presence of the HLA-B*1502 and methods which indirectly detect the presence of the HLA-B*1502 allele by, for example, assaying for the presence of an equivalent genetic marker. This interpretation of the claims is based on the teachings in the specification (e.g. page 6) the "The presence of the allele of interest can also be determined by detecting an an equivalent genetic marker of the allele, which is a genetic marker that is linked to the allele" and dependent claim 11 which recites "wherein the presence of the allele is determined by assaying for an equivalent genetic marker of the allele".

It is also noted that while the rejection of claims indicates some enablement with regard to the association of the detection of the 1502 allele or the Cw*0801 allele with and increased risk of SJS/TEN with CBZ, claim 1 (from which claims 3, 6, and 8-12 depend) recites only 'the presence of the HLA-B allele is indicative of a risk for an adverse drug reaction', which does not require that the detection of the allele is indicative of an increased risk.

Applicants have argued that the specification of the instant application is enabling for the analysis of all human subjects. Applicants argue (and disclose in the Declaration at part 7) that the subjects of study of the instant application included subjects from locations other than Taiwan and had places of birth other than Taiwan. The Declaration

indicates that the study subjects were decendents of Han Chinese. It is noted that the rejection indicates enablement for a Taiwanese subject where 'Taiwanese' is an indication of ethnicity, not necessarily, for example, place of birth or citizenship. It is not clear that the specification as originally filed has basis for language such as 'a patient descended from Han Chinese', or 'an Asian patient'.

Applicants particularly argue that the claimed methods are enabled for all human subjects pointing to (part 8 of the Declaration) a working model presented in Fig 2 of Hung et al which alleges that CBZ or its metabolites bind to an unknown peptide that is complexed with the 1502 molecule. Applicants argue that such a model indicates that finding the 1502 allele in any subject would be indicative of increased risk of SJS/TEN in response to CBZ. This is not found to be persuasive as the proposed working model of Hung et al is merely a hypothetical working model that is not necessarily supported by any actual biochemical, in vitro, or in vivo experimental results, data, or evidence that actually shows the 1502 molecule in fact participates in an interaction with CBZ that is required for development of SJS/TEN. And while applicants argue that it is difficult to find sufficient Caucasians with the 1502 allele who have taken CBZ to perform a meaningful study (Declaration part 11), and that even low frequency alleles can be useful genetic markers (Declaration part 13), the Examiner notes that there are no experimental results (not just merely a lack of significant results) indicating that, for example, a Caucasian with the 1502 allele would have SJS/TEN in response to CBZ. Further, the recent post-filing art of Alfirevic et al (2006) summarizes the issue of using 1502 as a marker in populations of different ethnicities:

> '...the linkage disequilibrium patterns of the major histocompatibility complex between Caucasians and Chinese individuals are likely to be different. An analogy can be drawn here with the strong association of *HLA-B*5701*with abacavir hypersensitivity in Caucasians, but not Africans' (p.816, left col., lns. 4-10).
>
> 'Although a strong association has been identified between *HLA B*1502* and CBZ-induced SJS in Chinese patients, it does not necessarily indicate that this locus is the causal variant given the high degree of linkage disequilibrium in the major histocompatibility complex' (p.817, right col., lns.7-13).

Thus without convincing evidence that the 1502 allele is in fact causative of SJS/TEN in response to CBZ or associated with SJS/TEN in response to CBZ in other populations, the instant specification is not considered enabling for assessing the risk of SJS/TEN in response to CBZ in populations of ethnicities other than those presented in the instant application.

It is further noted that the orginially filed specification and claims encompass methods comprising the determination of the presence of, for example, the HLA-B*1502 allele by indirect methods, though the rejection of claims indicates that the specification is not enabled for such methods that encompass the generic detection of equivalent genetic markers. And while the Declaration provides data regarding the drug phenytoin, the specific recitation of this element in the claims is objected to as non-elected subject matter.

Finally, the Remarks indicate that 'the CBZ and phenytoin in the claimed invention encompass their metabolites and analogs that have the same therapeutic applications as CBZ and phenytoin, respectively'. However, Applicants appear to be assigning a definition to the terms 'CBZ' and 'phenytoin' which is distinct from that

recognized in the art. The terms 'CBZ' and 'phenytoin' refer to only the particularly stated drugs and do not refer to or encompass metabolites or analogs of these drugs. The Examiner has required the election of only a particular drug, and not construed the claims to generically encompass, for example, methods for assessing the risk of patient for developing an adverse drug reation in response to any metabolite or analog of CBZ. In fact, the originally filed specification does not appear to have support for any drug analogs.

The rejection is MAINTAINED.

Response to the Declaration

4. The Declaration under 37 CFR 1.132 filed 09/18/2006 is insufficient to overcome the rejection of claims 1, 3, 6, 8-12, and 20-25 based upon lack of enablement under 35 USC 112 1st ¶ as set forth in the last Office action because:

As discussed in the Response to Remarks above, the declaration does not provide clear evidence that the 1502 allele would in fact be useful for assessing risk of CBZ-induced SJS/TEN in any non-Taiwanese population. The hypothetical working model of Hung et al, as described in the Declaration, does not amount to evidence of a causal relationship between the 1502 allele and CBZ-induced SJS/TEN. Furthermore, while the Declaration asserts that even low frequency alleles may be useful for diagnostic purposes, there is no showing of any instance in which, for example, a Caucasian person with CBZ-induced SJS/TEN has the 1502 allele.

It is noted that the Declaration (part 16 of the Declaration) does provide persuasive evidence (p-value and Odds Ratio with 95% confidence interval) that the HLA-Cw*0801 allele is indicative of an increased risk of CBZ-induced SJS/TEN. The rejection set forth in the Office Action has been changed to reflect this persuasive evidence.

Conclusion

5. No claim is allowable.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen Kapushoc
Art Unit 1634

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER